PATHWAYS FOR THE SYNTHESIS OF PYRIMIDINE AND PYRAN BASED HETEROCYCLIC DERIVATIVES: A CONCISE REVIEW

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Keywords: heterocycles, pyrimidines, pyrans, diethyl malonate, malononitrile.

Pyrimidines and pyrans are the special class of heterocyclic compounds with a broad spectrum of biological activities such as anticancer, antiviral, antibacterial, antioxidant, antiallergic and antidepressant. The use of pyran derivatives is not only limitted in cosmetics, pigments and biodegradable agrochemicals but also constitute a structural unit of many natural products. Therefore researchers have synthesized these condensed heterocycles through different complex pathways as target structures for biological studies. This review focuses on the various strategies followed for the convenient synthesis of pyrimidine and pyran based heterocyclic compounds. The steps included condensation followed by cyclization or MCR, either in a step-wise manner or in one pot has been achieved successfully to obtain these two classes of heterocycles under different conditions. Diethyl oxalate, diethyl malonate, malononitrile and ethyl cyanoacetate are the most common reagents used for the synthesis of pyrimidines and pyrans appended on different heterocyclic skeletons.

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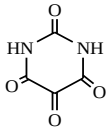
Introduction

Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process and analysis of drugs in late development or in the market shows that 68 % of them are heterocycles.[1,2] hence it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received significant attention in the recent years. Pyrimidine or 1,3-diazine (**1**) is a 6-membered aromatic heterocycle with two nitrogen atoms in the ring at 1,3-positions.[3] It may be regarded as being derived from benzene by the replacement of two *meta* "CH" groups by "N". The pyrimidine ring system has wide occurrence in nature as substituted and fused ring derivatives, like the nucleotides, thiamine and alloxan (**2**).[4] It is also found in many synthetic compounds such as barbiturates and the HIV drug, Zidovudine.

(**1**)



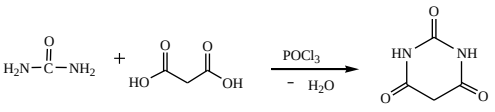
(**2**)

Its derivatives have been known to display a wide range of pharmacological activities as regards the tyrosine kinase domain of epidermal growth factor receptor,[5] 5-phosphoribosyl-1-pyrophosphate synthetase[6] and dihydrofolate reductase[7] have been fully demonstrated. Numerous reports delineate the antitumour, antiviral, antioxidant and hepatoprotective activity of these compounds.[8-11] Similarly, in recent years, considerable attention has been focused on the development of new methodologies to synthesize many kinds of pyrazole based pyrimidine ring system.[12] Indeed, these compounds are, by now widely recognized as important organic materials showing interesting biological activities.[13] In addition, these fused heterocyclic systems like pyrazolopyridopyrimidines, pyrazoloquinolines and pyrazolopyridines present the interesting biological properties such as virucidal, anticancer, fungicidal, bactericidal and vasodilatory activities.[14]

The pyrimidine heterocyclic core is an important subunit because of its widespread abundance in the basic structure of numerous natural products.[15] A number of synthetic pharmacophores based upon the pyrimidyl structure exhibit antibacterial, anticancer, anti-HIV-1 and antirubella virus activities.[16-18] The fused pyrimidine ring systems containing substituted six-membered ring have been proved to have cytotoxic nature[19,20] and the reason for the bio-toxicity of the pyrimidine heterocycles may be attributed to the presence of a subunit such as >N-CS-N<.[21] As such the development of clinically useful anticancer drug (5-fluorouracil)[22] and antiviral drugs (AZT, DDI, BVDU)[23-25] has renewed the interest in the synthetic manipulation of pyrimidine derivatives.[26] Here in we report the different strategies including cyclization, multi component reaction, reduction and oxidation approaches for the synthesis of pyrimidine and pyran based heterocycles.

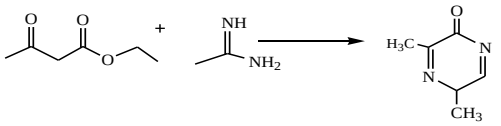
Synthesis of pyrimidine derivatives

Although pyrimidine derivatives such as uric acid and alloxan were known in the early 19th century, a laboratory synthesis of a pyrimidine was not carried out until 1879,[4] when Grimaux[27] reported the preparation of barbituric acid (**3**) from urea and malonic acid in the presence of phosphorus oxychloride.



3

The systematic study of pyrimidines began in 1884 with Pinner[28] who synthesized 3,5-dimethyl-5H-pyrazin-2-one (**4**) by condensing ethyl acetoacetate with acetamidine. Pinner[29] first proposed the name "pyrimidin" in 1885 which later got modified as "pyrimidine".



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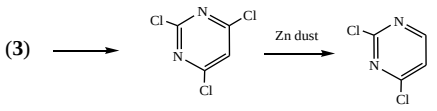
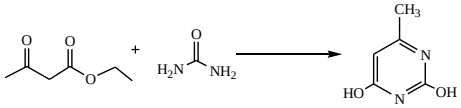
Gabriel and Colman[30] in 1900 reported the conversion of barbituric acid (**3**) into trichloropyrimidine (**5**) by $POCl_3$. The compound (**5**) upon selective reduction yielded dichloropyrimidine (**6**).



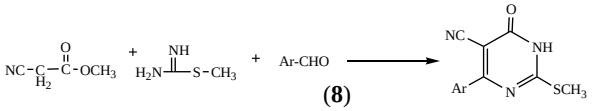
(**5**) (**6**)

Benhard[31] reported the reaction of ethyl acetoacetate with urea that yielded a pyrimidine derivative (4-methyluracil) (**7**) in better amounts.



(**7**)

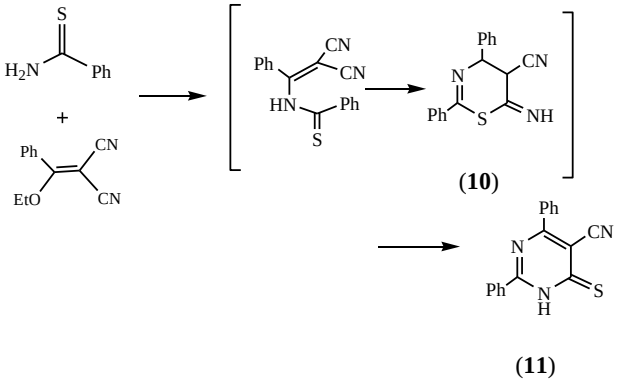
Hussain and co-workers[32] reported that heating the mixture of methyl cyanoacetate, S-methyl isothiourea and aldehydes (**8a-d**) yielded corresponding 4-aryl-5-cyano-2-methylthio-6-oxopyrimidine derivatives (**9a-d**).



(**8**) (**9**)

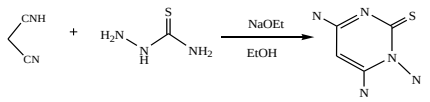
Ar: (**a**) C_6H_5, (**b**) *p*-NO_2-C_6H_4, (**c**) *o*-CH_3O-C_6H_4, (**d**) *o*-NO_2-C_6H_4

Soto and co-workers[33] reported the reaction of thiobenzamide with 3-ethoxy-3-phenyl-2-cyanoacrylonitrile (**10**) in presence of sodium isopropoxide in 2-propanol to afford 5-cyano-2,6-diphenyl-4-thioxo-3,4-dihydro-pyrimidine (**11**) through formation of the 3-phenyl-2-cyano-3-thiobenzamide acrylonitrile as an intermediate.



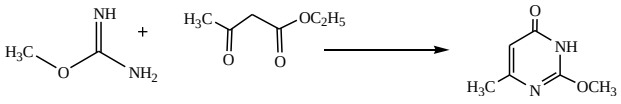
(**10**) (**11**)

Taylor and Morrison[34] reported the synthesis of 1,4,6-triamino-2(2H)-pyrimidine-2-thione (**12**) by reacting malononitrile with thiosemicarbazide in presence of sodium ethoxide in ethanol.



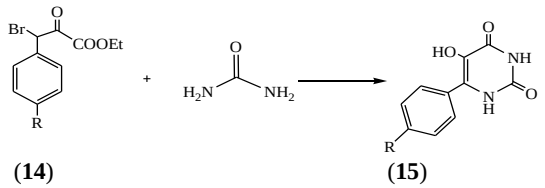
12

Botta and co-workers[35] reported the synthesis of 2-methoxy-6-methyl-3(2H)-pyrimidin-4-one (**13**) after reacting ethyl acetoacetate and O-methylisourea in an aqueous medium.



(**13**)

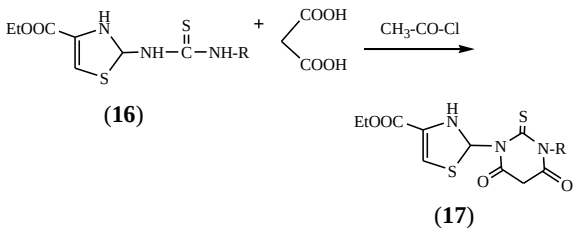
Andereichikov and co-workers[36] reported the synthesis of uracil derivatives (**15a-d**) by the reaction of aryl substituted bromopyruvate esters (**14a-d**) with urea.



(**14**) (**15**)

R: (**a**) OCH_3, (**b**) OH, (**c**) Cl, (**d**) H

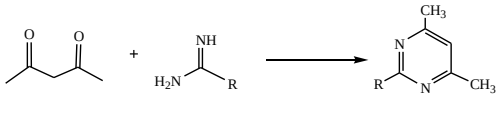
El-Subbagh[37] reported the synthesis of pyrimidine derivative (**17a**,**b**) by reacting thiazolyl thiourea derivatives (**16a**,**b**) with malonic acid in the presence of acetyl chloride.



(**16**) (**17**)

R: (**a**) CH_3, (**b**) C_2H_5

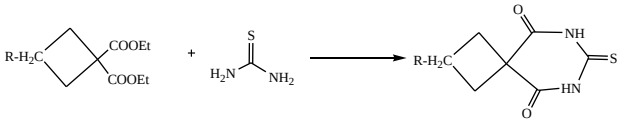
Bowman and co-workers[38] reported that acetyl acetone condensed with acetamidine derivatives (**18a-e**) and gave corresponding pyrimidine derivatives (**19a-e**) in good yields.



(**18**) (**19**)

R: (**a**) NH-C_6H_5, (**b**) SH, (**c**) NH-$C_6H_4CH_3$, (**d**) $NHNH.NO_2$, (**e**) C_2H_5

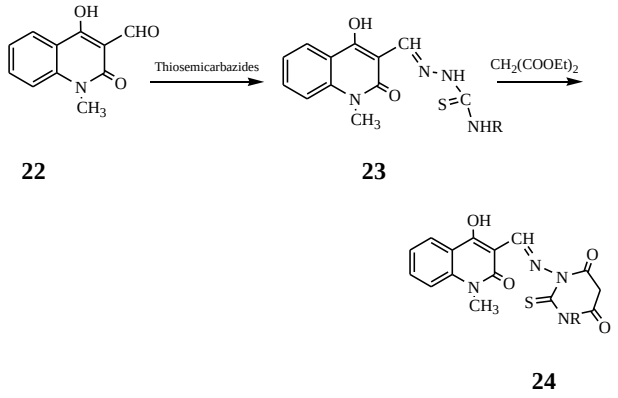
Yossef and co-workers[39] reported the reaction of 1,1-cycloalkane dicarboxylic acid diethyl esters (**20a-c**) with thiourea which gave *spiro*-barbituric acid derivatives (**21a-c**).



(**20**) (**21**)

R: (**a**) CH_3, (**b**) C_2H_5, (**c**) isopropyl

Mohamed[40] reported the reaction of 1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde (**22**) with thiosemicarbazides to yield desired thiosemicarbazones (**23a-d**). These thiosemicarbazones then reacted with diethyl malonate which resulted into corresponding pyrimidine derivatives (**24a-d**) in good yields.

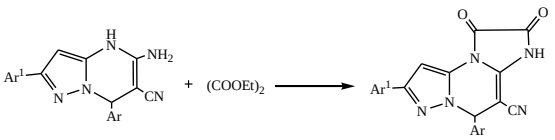


22 **23**

24

R: (**a**) H, (**b**) C_6H_5, (**c**) *p*-$CH_3OC_6H_4$,(**d**) H_2C=CH-CH_2

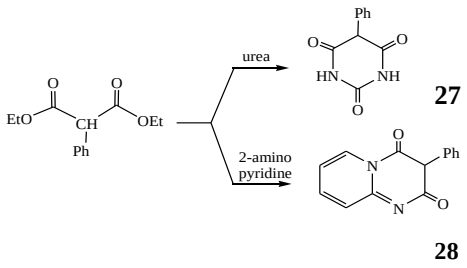
Eldin and Attaby[41] reported the reaction of pyrazole[3,2-*b*]pyrimidine derivatives (**25a-p**) with diethyl oxalate which yielded imidazo[1,2:3',4']pyrazole[3,2-*b*]pyrimidine derivatives (**26a-p**) in good yields.



(**25**) (**26**)

Ar, Ar[1]: (**a**) C_6H_5, C_6H_5, (**b**) *p*-Cl-C_6H_4, C_6H_5 (**c**) *p*-$CH_3OC_6H_4C_6H_5$, C_6H_5, (**d**) *p*-$O_2NC_6H_4$, C_6H_5, (**e**) C_4H_3O-*α*, C_6H_5, (**f**) C_4H_3S-*α*,C_6H_5, (**g**) C_6H_5, *p*-$CH_3C_6H_4$, (**h**) *p*-ClC_6H_4, *p*-$CH_3C_6H_4$, (**i**) *p*-$CH_3OC_6H_4$, *p*-$CH_3C_6H_4$, (**j**) *p*-$NO_2C_6H_4$, *p*-$CH_3C_6H_4$, (**k**) C_4H_3O-*α*, *p*-$CH_3C_6H_4$, (**l**) C_4H_3S-*α*, *p*-$CH_3C_6H_4$, (**m**) C_6H_5, *p*-BrC_6H_4, (**n**) *p*-ClC_6H_4, *p*-BrC_6H_4, (**o**) *p*-$CH_3OC_6H_4$, *p*-BrC_6H_4, (**p**) C_4H_3O-*α*, *p*-BrC_6H_4.

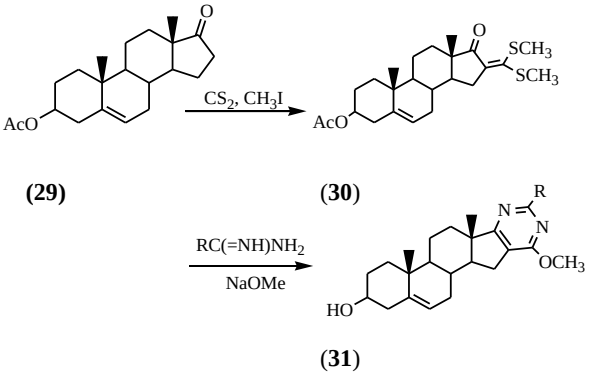
Stadlbauer and co-workers[42] reported the reaction of diethyl malonate with urea and 2-aminopyridine which gave barbituric acid derivative (**27**) and pyrido[1,2-*a*]pyrimidine-2,4-dione derivative (**28**), respectively in better yields.



27

28

Peseke and co-workers[43] reported the reaction of androstenolone acetate (**29**) with CS_2 and CH_3I that yielded 3*β*-acetoxy-16-[bis(methylthio)methylene]androst-5-en-17-one (**30**) which later reacted with different amidines in presence of sodium methoxide to provide corresponding steroidal pyrimidine derivatives (**31a-e**).

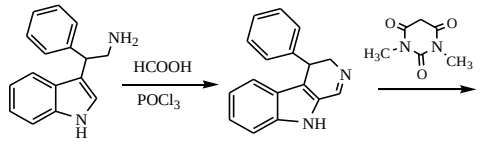


(**29**) (**30**)

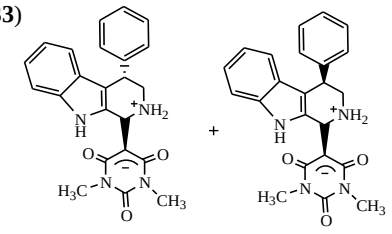
(**31**)

R: (**a**) H, (**b**) C_2H_5, (**c**) C_6H_5, (**d**) NH_2, (**e**) OCH_3

Semenov *et al.*[44] reported the reaction of *β*-phenyl-tryptamine (**32**) with formic acid under Bischler-Napieralski conditions that yielded 4-phenyl-3,4-dihydro-*β*-carboline (**33**) which upon reaction with 1,3-dimethylbarbituric acid provided two diastereomers of substituted pyrimidinones [**34** (*RR*), **35** (*RS*)].



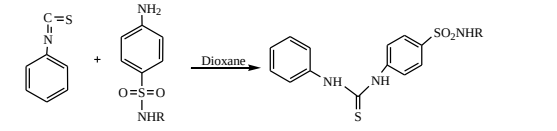
(**32**) (**33**)



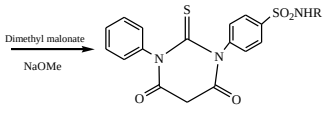
(**34**) (**35**)

Bawazir and co-workers[45] reported the reaction of phenylisothiocyanate (**36**) with sulfa drugs (**37a-c**) in 1,4-dioxane that yielded N,N'-disubstituted thiourea derivatives

(**38a-c**) which later on reaction with dimethyl malonate in presence of sodium methoxide provided corresponding 1,3-disubstituted thiobarbituric acid derivatives (**39a-c**).



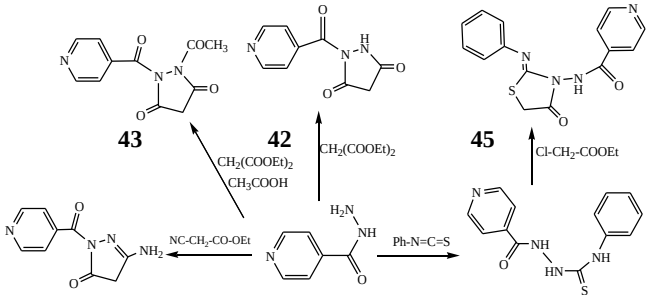
(36) **(37)** **(38)**



(39)

R: (**a**) H, (**b**)  , (**c**) 

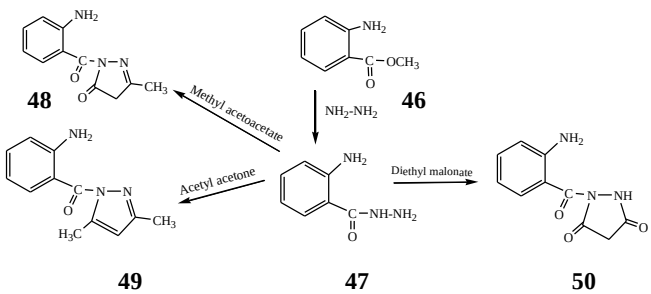
Parashar and co-workers[46] reported the reaction of isonicotinohydrazide (**40**) with ethyl cyanoacetate, diethyl malonate, diethyl malonate with acetic acid and phenylisothio- cyanate, which gave 3-amino-1-isonicotinoyl-1H-pyrazol-5(4H)-one (**41**), 1-isonicotinoyl-pyrazolidine-3,5-dione (**42**), 1-acetyl-2-isonicotinoyl-pyrazolidine-3,5-dione (**43**), 1-isonicotinoyl-4-phenyl-thiosemicarbazide (**44**), respectively. The compound (**44**) on further reaction with ethyl chloroacetate gave N-(4-oxo-2-(phenylimino)thiazolidin-3-yl) isonicotinamide (**45**).



43 **42** **45**

41 **40** **44**

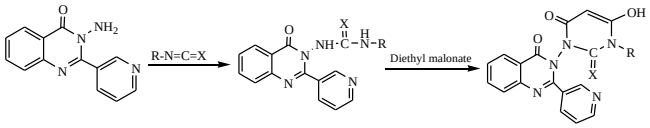
Hassan[47] reported the reaction of methyl anthranilate (**46**) with hydrazine hydrate that gave 2-aminobenzhydrazide (**47**) which in turn on reaction with methyl acetoacetate, acetyl acetone and diethyl malonate, yielded (2-amino benzoyl)-3-methyl-1H-pyrazole-5-(4H)-one (**48**), (2-aminobenzoyl)(3,5-dimethyl-1H-pyrazole-1-yl)methanone (**49**) and (2-aminobenzoyl)pyrazolidine-3,5-dione (**50**), respectively in good amounts.



48 **46**

49 **47** **50**

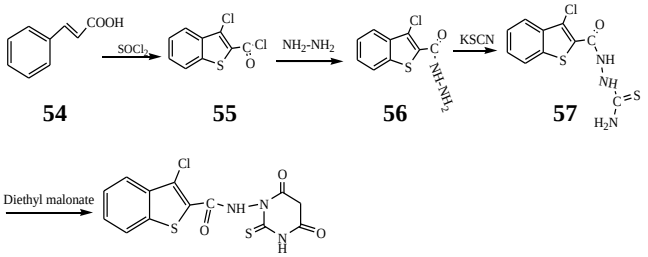
Abbas and co-workers[48] reported the reaction of 3-amino-2-(pyridin-3-yl)-4-quinazolinone (**51**) with *p*-hydroxy-phenyl isocyanate and phenyl isothiocyanate provided 1-(4-oxo-2-(pyridin-3-yl)quinazolin-3(4H)-yl)-3-phenylurea (**52a**) and 1-(4-oxo-2-(pyridin-3-yl) quinazolin-3(4H)-yl)-3-phenylthiourea (**52b**). The compounds (**52a** and **52b**) upon reaction with diethyl malonate and after keto-enol tautomerism, yielded 6-hydroxy-3-(4-oxo-2-(pyridin-3-yl)-quinazolin-3-(4H)-yl)-1-phenylpyrimidine-2,4-(1H,3H)-di-one (**53a**) and 3-(4-hydroxy-6-oxo-3-phenyl-2-thioxo-2,3-dihydropyrimidin-1(6H)-yl)-2-(pyridin-3-yl)quinazolin-4-(3H)-one (**53b**).



(51) **(52)** **(53)**

X: R: (**a**) O, C_6H_5, (**b**) S, C_6H_4OH-p

Naganagowda and co-workers[49] reported the synthesis of 3-chloro-1-benzothiophene-2-carbonylchloride (**55**) from cinnamic acid (**54**). The compound (**55**) reacted with hydrazine and gave 3-chloro-1-benzo[*b*]thiophene-2-carboxylic acid hydrazide (**56**) which on reaction with potassium thiocyanate provided 2-[(3-chloro-1-benzo[*b*]thiophen-2-yl)carbonyl]hydrazine carbothioamide (**57**) which on reaction with diethyl malonate yielded 3-chloro-N(4,6-dioxo-2-thioxotetrahydropyrimidin-1(2H)-yl)-1-benzothiophene-2-carboxamide (**58**).

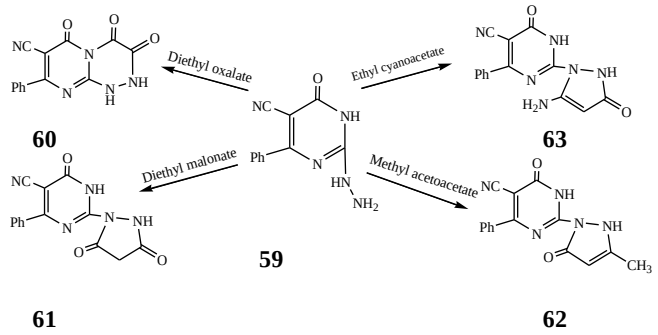


54 **55** **56** **57**

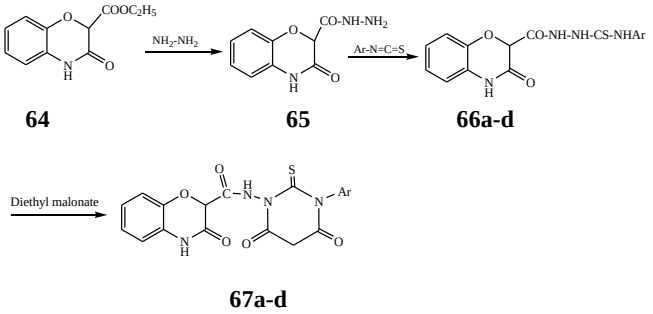
58

El-zahar and co-workers[50] reported the reaction of 2-hydrazino-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbo-nitrile (**59**) with diethyl oxalate, diethyl malonate, methyl acetoacetate and ethyl cyanoacetate that provided corresponding 3,4,6-trioxo-8-phenyl-tetrahydro-2H-pyrimi-do[2,1-*c*][1,2,4]triazine-7-carbonitrile (**60**), 2-(3,5-dioxo-pyrazolidin-1-yl)-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile (**61**), 2-(3-methyl-5-oxo-2,5-dihydro-pyrazol-1-yl)-6-oxo-4-phenyl-1,6-dihydropyrimidinecarbonitrile (**62**) and 2-(5-amino-3-oxo-2,3-dihydro-pyrazol-1-yl)-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile (**63**), respectively, in good yields.

Dabholkar and Gavande[51] reported the reaction of 2H, 4H-2-ethoxycarbonyl-3, 4-dihydro-3-oxo-1,4-benzoxazine (**64**) with hydrazine and provided 2H, 4H-2-hydrazino carbonyl-3,4-dihydro-3-oxo-1,4-benzoxazine (**65**) which upon reaction with arylisothiocyanate derivatives yielded 2H,4H-2-[(4'-substituted)arylthiosemicarbazino]carbonyl-3,4-di-hydro-3-oxo-1,4-benzoxazine derivatives (**66a-d**).

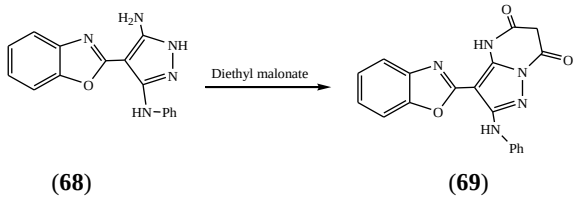


The compounds (**66a-d**) later on reaction with diethyl malonate and gave 2H,4H-2-[5'H-5'-dihydro-2'-thioxo-3'-aryl-4',6'-dioxo-1,3-diazine]aminocarbonyl-3,4-di-hydro-3-oxo-1,4-benzoxazines (**67a-d**).

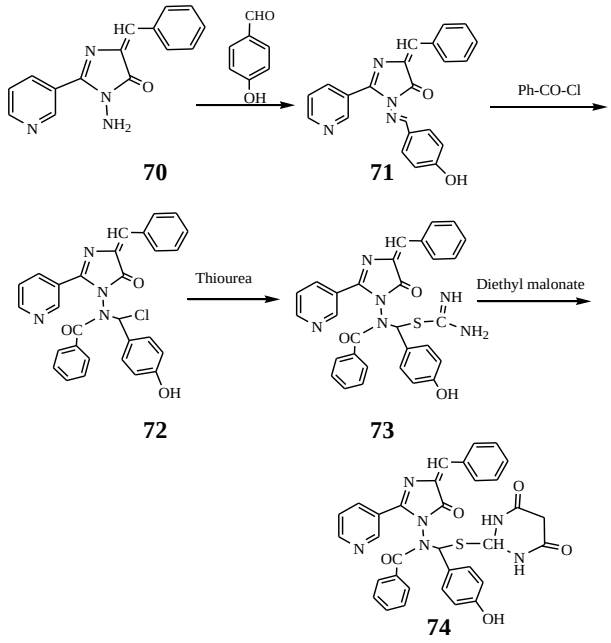


Ar: (a) Ph, (b) $C_6H_4CH_3$, (c) $C_6H_4NO_2$, (d) $C_6H_3(NO_2)_2$

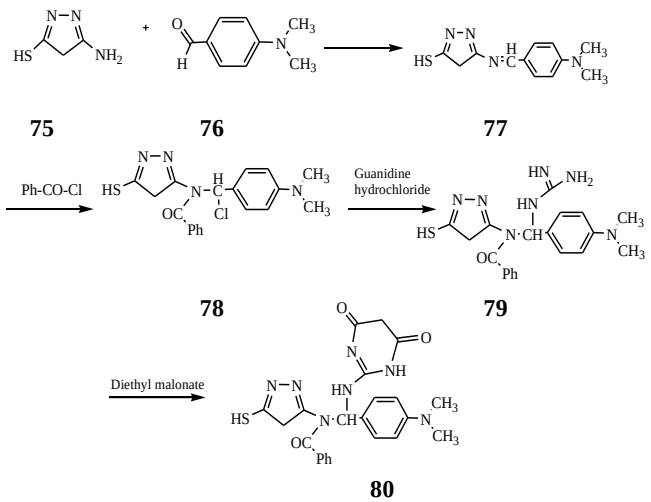
Wahab and Mohamed[52] reported the reaction of N-[3-amino-4-(benzoxazol-2-yl)pyrazol-5-yl]phenylamine (**68**) with diethyl malonate which provided 3-benzoxazol-2-yl-2-phenylamino-4H-pyrazolo[1,5-*a*]pyrimidine-5,7-dione (**69**) in 80 % yield.



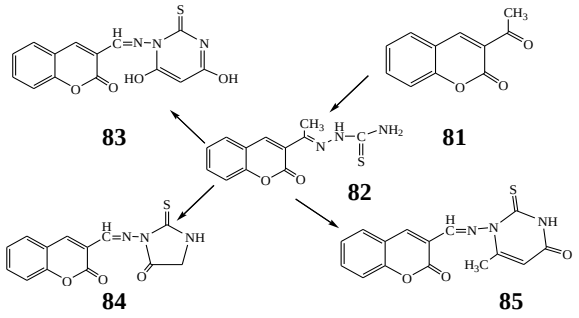
Abodi and co-workers[53] reported the reaction of 3-amino-5-(benzylidene)-2-(pyridin-3-yl)-3,5-dihydro-4H-imidazol-4-one (**70**) with *p*-hydroxybenzaldehyde which gave 5-(benzylidene)-3-[(*p*-hydroxybenzylidene)amino]-2-(pyridin-3-yl)dihydro-4H-imidazol-4-one (**71**). The compound (**71**) reacted with benzoyl chloride and provided N-[chloro(4'-phenyl)methyl]-N-[4'-*p*-hydroxybenzylidene-5'-oxo-2-(pyridin-3-yl)-4,5-dihydro-1H-imidazol-1-yl]benzamide (**72**). The compound (**72**) later upon reacted with thiourea yielded 4'-phenyl-{[4'-(4'-benzylidene-5'-oxo-2-(pyridin-3-yl)-4,5-dihydro-1H-imidazol-1-yl](*p*-hydroxybenzoyl)amino}methyl carbamimidothioate (**73**). The compound (**73**) in turn reacted with diethyl malonate yielded N-{1-[(4",6"-dioxotetrahydropyrimidin-2-yl)sulfanyl]benzyl}-N-[4-*p*-hydroxybenzylidene-5'-oxo-2-(pyridin-3-yl)-4,5-dihydro-1H-imidazol-1-yl-benzamide (**74**).



Drea and co-workers[54] reported the reaction of 5-amino-3-mercaptopyrazole (**75**) with 4-dimethylaminobenzaldehyde (**76**) which gave 5-(4'-dimethylamino)benzylidene)amino-3-mercaptopyrazole (**77**). The compound (**77**) on reaction with benzoyl chloride provided 5-(4'-dimethylamino)-chlorobenzylidene)-N-(benzoyl)amino-3-mercaptopyrazole (**78**). The compound (**78**) reacted with guanidine hydrochloride and yielded 5-{(4'-dimethylamino)-benzylidene)-N-(benzoyl)-N-(guanidino)}-amino-3-mercaptopyrazole (**79**) which later on reaction with diethyl malonate gave 5-{(4'-dimethylamino)benzylidene)-N-(benzoyl)(4,6-dioxotetrahydropyrimidin-2-ylamino)methyl)-}amino-3-mercaptopyrazole (**80**).

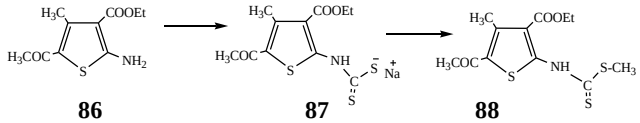


Hasanen[55] reported the reaction of 3-acetylcoumarin (**81**) with thiosemicarbazide that provided 3-acetylcoumarin thiosemicarbazone (**82**) which reacted with diethyl malonate, chloroethyl acetate and ethyl acetoacetate to yield corresponding 4,6-dihydroxy-1-(coumarin-3-ylethylidene)-aminopyrimidin-2-thione (**83**), 3-(coumarin-3-ylethylidene)amino-2-thioxoimidazolidin-4-one (**84**) and 6-methyl-1-(coumarin-3-ylethylidene)amino-2-thioxopyrimidin-4-one (**85**) in better yields.

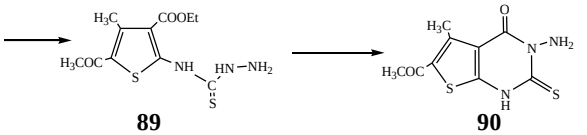


83 **81** **82** **84** **85**

Hafez and co-workers[56] reported the reaction of 5-acetyl-3-ethyl-2-amino-4-methylthiophene carboxylate (**86**) with CS_2 which gave methyl N-(4-methyl-5-acetyl-3-carboxyethylthiophene)dithiocarbamate (**88**). The compound (**88**) reacted with hydrazine and yielded methyl N-(4-methyl-5-acetyl-3-carboxyethylthiophene)thiosemicarbazide (**89**). The compound (**89**) in warmed ethanolic sodium hydroxide solution cyclized and gave 3-amino-6-acetyl-5-methyl-2-thioxothieno[2,3-*d*]pyrimidin-4-one (**90**).

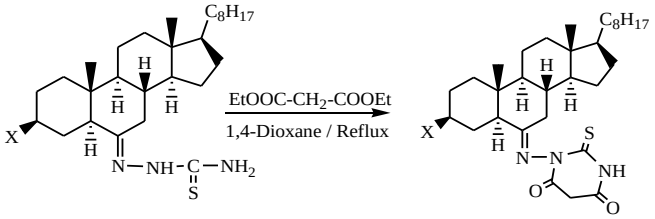


86 **87** **88**



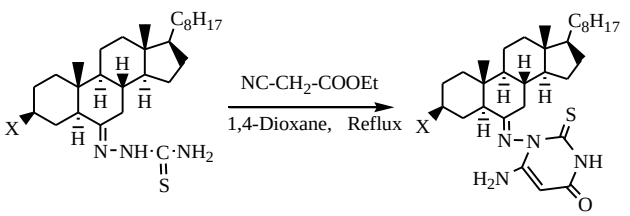
89 **90**

Shamsuzzaman and co-workers[57] reported the reaction of steroidal thiosemicarbazones (**91-93**) with diethyl malonate that provided steroidal pyrimidinones (**94-96**) in better yields.



X= OAc (**91**), Cl (**92**), H(**93**) X=OAc (**94**), Cl (**95**), H (**96**)

Shamsuzzaman and co-workers[58] also reported another set of reaction in which steroidal thiosemicarbazones (**91-93**) reacted with ethyl cyanoacetate and yielded differently substituted steroidal pyrimidines (**97-99**) in sufficient amounts.



X=OAc (**91**), Cl(**92**), H (**93**) X=OAc (**97**), Cl (**98**), H (**99**)

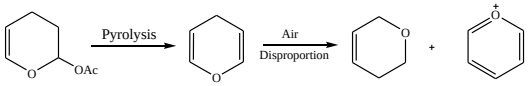
Synthesis of pyran derivatives

Pyran is a six membered non-aromatic ring consisting of five carbon atoms, one oxygen atom and two double bonds. The term pyran is also often applied to the saturated ring analog, which is more properly referred to as tetrahydropyran (oxane). There are two isomers of pyran that differ by the location of the double bonds. In 2H-pyran (**100**), the saturated carbon is at position 2 while as in 4H-pyran (**101**), the saturated carbon is at position 4.

(**100**) (**101**)

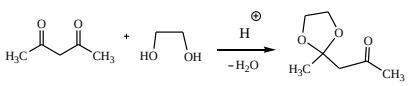
They are not only used in cosmetics, pigments and biodegradable agrochemicals[59,60] but also constitute a structural unit of many natural products.[61] These compounds have been reported to possess various pharmacological activities such as antiallergic, antitumor and antibacterial.[62,63]

Masamune and Castellucci[64] in 1962 first isolated and characterized 4H-pyran by the pyrolysis of 2-acetoxy-3,4-dihydro-2H-pyran (**102**). It was found unstable in the presence of air so disproportionated to the dihydropyran (**103**) and the pyrylium ion (**104**).

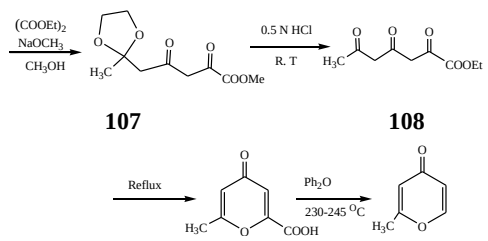


(**102**) (**101**) (**103**) (**104**)

Dorman[65] in 1967 reported the reaction of acetyl acetone (**105**) with ethylene glycol which gave 2-methyl-2-acetonyl-1,3-dioxolan (**106**). The compound (**106**) was acylated with diethyl oxalate in presence of sodium methoxide formed methyl 5-(2-methyl-[1,3]dioxolan-2-yl)-2,4-dioxopentanoic acid methyl ester (**107**). The compound (**107**) was treated with 0.5 N HCl to give intermediate triketone (**108**). The compound (**108**) was refluxed to complete ring closure forming 6-methyl-4H-pyran-4-one-2-carboxylic acid (**109**) which on subsequent decarboxylation yielded 2-methyl-4H-pyran-4-one (**110**).



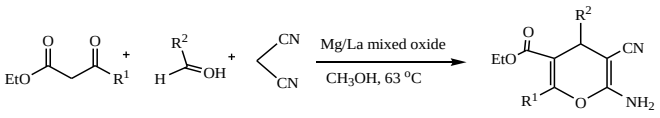
105 **106**



107 **108**

(109) **(110)**

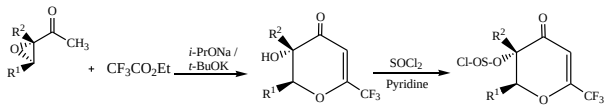
Lingaiah and co-workers[66] reported an efficient synthesis of polyfunctionalized 4H-pyrans (**113a-h**) by one pot condensation of active methylenic diketo compounds (**111a-h**), aldehydes (**112a-h**) and malononitrile using basic Mg/La mixed oxide as catalyst.



111 **112** **113**

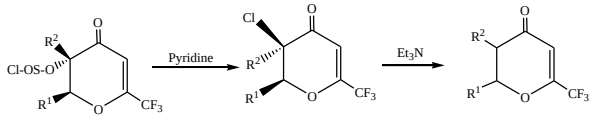
R[1]: (a) C_2H_4Br, (b) C_2H_5, (c) C_3H_7, (d) CH_2Cl, (e) CH_2Br, (f) C_6H_4Cl, (g) C_6H_4Br, (h) CH_2I, **R[2]:** (a) C_6H_5, (b) 4-NO_2-C_6H_4, (c) 3-$C_6H_4NO_2$, (d) 4-Cl-C_6H_4, (e) 4-CNC_6H_4, (f) 4C_6H_4OH, (g) 4-MeC_6H_4, (h) 4-MeOC_6H_4

Tyvorskii and co-workers[67] reported the reaction of oxiranes (**114a-e**) with ethyl perfluoroalkanoate in presence of sodium *iso*-propoxide or potassium *tert*-butoxide that gave hydroxypyranones (**115a-e**). The hydroxypyranones upon reaction with thionyl chloride in dry pyridine yielded chlorosulfites (**116a-e**). These sulphites upon refluxing in presence of pyridine provided chlorosubstituted pyranones (**117a-e**) which on reaction with triethylamine yielded 2-perfluoroalkyl-4H-pyran-4-ones (**118a-e**).



114 **115** **116**

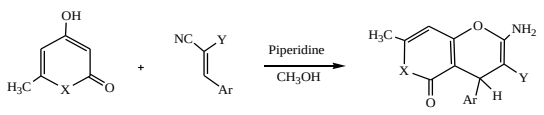
R[1]: (a) H, (**b**) H, (**c**) CH_3, (**d**) CH_2Cl, (**e**) CH_2I, **R[2]**: (**a**) CH_3, (**b**) Ph, (**c**) CH_3, (d) CH_3, (**e**) Ph



116 **117** **118**

R[1]: (a) H, (**b**) H, (**c**) CH_3, (**d**) CH_2Cl, (**e**) CH_2I, **R[2]**: (**a**) CH_3, (**b**) Ph, (**c**) CH_3, (d) CH_3, (**e**) Ph

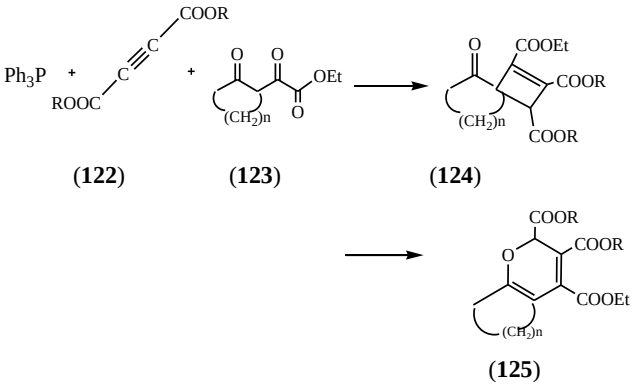
Stoyanov and co-workers[68] reported the reaction of 4-hydroxy-6-methyl-pyranone and pyridinone derivatives (**119a-c**) with Knoevenagel products (**120a-c**) in presence of piperidine in methanol to yield substituted 2-amino-4H, 5H-pyrano[4,3-*b*]pyran-5-ones (**121a-c**).



119 **120** **121**

X: (a) O, (**b**) NH, (**c**) NCH_2Ph, **Ar: (a)** Ph, (**b**) Ph, (**c**) NO_2Ph, **Y: (a)** $COOCH_3$, (**b**) CN, (**c**) $COOC_2H_5$

Yavari and Bayat[69] reported that dialkylacetylene dicarboxylates (**122a-d**) reacted smoothly with triphenyl phosphine and ethyl oxo(2-oxocycloalkyl)ethanoates (**123a-d**) via intramolecular Wittig reaction to produce *spiro*cyclobutene derivatives (**124a-d**). These *spiro* systems underwent electrocyclic ring-opening reaction to produce electron-deficient 1, 3-dienes which spontaneously cyclized to 2H-pyran derivatives (**125a-d**).

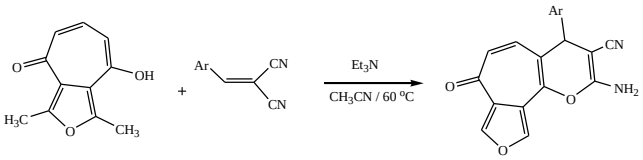


(**122**) (**123**) (**124**)

(**125**)

R: (a) Me, (**b**) Et, (**c**) *i*Pr, (**d**) *i*Bu, **n: (a)** 3, (**b**) 4, (**c**) 5, (**d**) 9

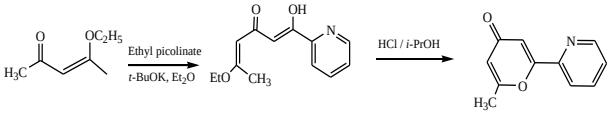
Arseneva and Arsenev[70] reported that 8-hydroxy-1,3-dimethyl-4H-cyclohepta[*c*]furan-4-one (**126**) on reaction with arylidenemalononitriles (**127a-h**) gave the corresponding condensed 2-amino-4H-pyrans (**128a-h**) in good yields.



126 **127** **128**

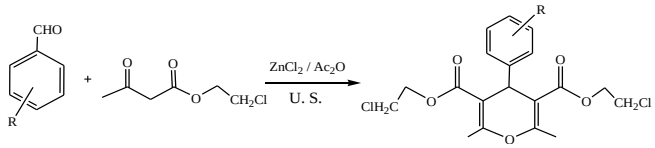
Ar (**a**) $Cl_2C_6H_3$, (**b**) FC_6H_4, (**c**) ClC_6H_4, (**d**) BrC_6H_4, (**e**) EtO-C_6H_4, (**f**) MeO-C_6H_4, (**g**) MeS-C_6H_4, (**h**) thienyl

Bobrov and Tyvorskii[71] reported the synthesis of 6-methyl-2-(2-pyridyl)-4H-pyran-4-one (**131**). The pyranone precursor (5-ethoxy-1-hydroxy-1-pyridin-2-yl-hexa-1,4-dien-3-one) (**130**) was prepared by Claisen condensation of acetyl acetone enol ether (**129**) with ethyl picolinate.



(**129**) (**130**) (**131**)

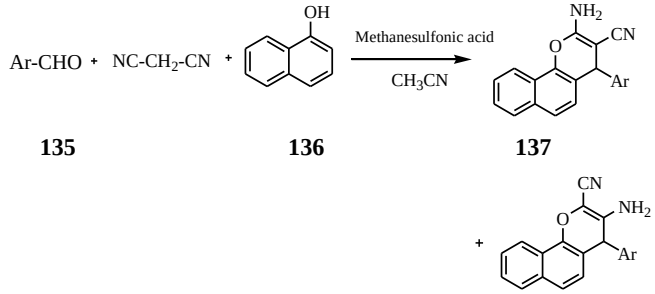
Ni and co-workers[72] reported the reaction of aromatic aldehydes (**132a-j**) with 3-oxo-butyric acid-2-chloroethyl ester (**133**) in acetic anhydride in presence of zinc chloride, which was irradiated by an ultrasonic processor at 50 °C and 100 W to yield substituted 4-aryl-4H-pyran-3,5-dicarboxylates (**134a-j**).



132 **133** **134**

R: (a) 2-F, (**b**) 2,4-$(CH_3)_2$, (**c**) 4-Br, (**d**) 4-OC_2H_5, (**e**) 2,4-Cl, Br, (**f**) 2,4-Cl, I, (**g**) 4-F, (**h**) 2,4-NO_2,CH_3, (**i**) 2,4-$(OH)_2$, (**j**) 3-Br

Heravi and co-workers[73] reported one-pot, three component reaction of aromatic aldehydes (**135a-e**), malononitrile and *α*-naphthol (**136**) in presence of methanesulfonic acid to yield two isomers of 2-amino-4H-chromenes **137a-e** and **138a-e** in very good yields.

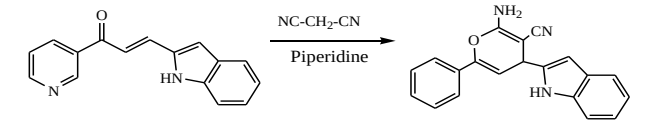


135 **136** **137**

138

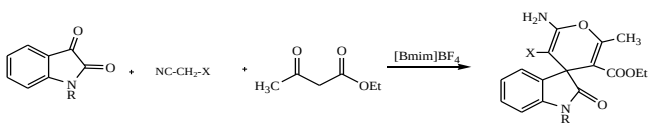
Ar: (a) $Cl_2C_6H_3$, (**b**) $(NO_2)_2C_6H_3$, (**c**) $(MeO)_2C_6H_3$, (**d**) $FClC_6H_3$, (**e**) $ClNO_2C_6H_3$,

El-Latif and co-workers[74] reported the reaction of 3-*β*-indolylacryloylpyridine (**139**) with malononitrile in presence of piperidine to yield 2-amino-4-(3-indolyl)-6-(3-pyridyl)-pyran-3-carbonitrile (**140**).



(**139**) (**140**)

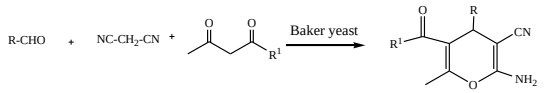
Moghadam and Miri[75] reported the reaction of isatins (**141a-b**), malononitrile or ethyl cyanoacetate and 1, 3-dicarbonyl compound in the ionic liquid to yield *spiro*[4H-pyranoxindole] derivatives (**142 a-d**) in better amounts.



141 **142**

R: (**a**) H, (**b**) H (**c**) Bu, (**d**) Bu, **X: (a)** CN, (**b**) COOEt, (c) CN, (d) COOEt

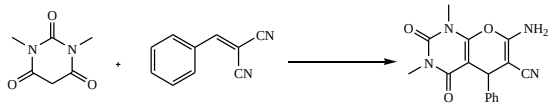
Pratap and co-workers[76] reported the Baker's yeast catalyzed one-pot three-component cyclocondensation of aryl aldehydes (**143a-g**), malononitrile and *β*-dicarbonyls (**144a-c**) in dimethylacetamide solvent to obtain polyfunctionalized 4H-pyrans (**145a-g**).



(**143**) (**144**) (**145**)

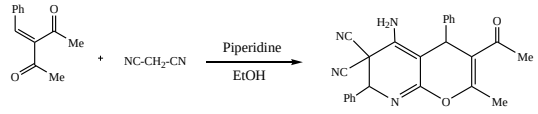
R: (**a**) $(MeO)_2C_6H_3$, (**b**) $Cl_2C_6H_3$, (**c**) $3\text{-}ClC_6H_4$, (**d**) $4\text{-}HOC_6H_4$, (**e**) $4\text{-}FC_6H_4$, (**f**) 3-pyridyl, (**g**) $4\text{-}CH_3C_6H_4$, **R[1]**: (**a**) OEt, (**b**) Me, (**c**) OMe, (**d**) OEt, (**e**) Me, (**f**) OMe, (**g**) OEt

Seeliger and co-workers[77] have reported the formation of dihydropyrano[2,3-*c*]pyrimidinedione (**148**) in 80 % yields by the reaction of 1,3-dimethylbarbituric acid (**146**) with arylidenemalononitrile (**147**) upon protonation.



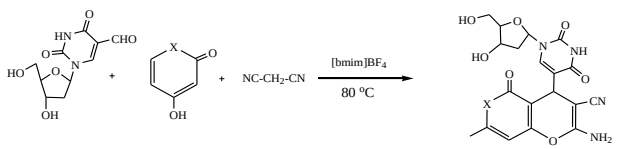
146 **147** **148**

Martin and co-workers[78] reported the synthesis of pyrano[2,3-*b*]pyridine derivative (**150**) from malononitrile and 2-benzylidene-1,3-diketone (**149**). The compound **149** is easily accessible via Knoevenagel condensation of benzaldehyde and pentan-2,4-dione.



149 **150**

Feng and co-workers[79] reported the multi-component reactions of nucleoside (**151**), 4-hydroxy-2-pyranone (**152a**) or 4-hydroxy-pyridin-2(1H)-one (**152b**) and malononitrile in presence of ionic liquid to provide the efficient synthesis of pyrano[4,3-*b*]pyran nucleoside derivative (**153a**) and pyrano[3,2-*c*]pyridine nucleoside derivative (**153b**) which were also found as potential antiviral and anti-leishmanial agents.

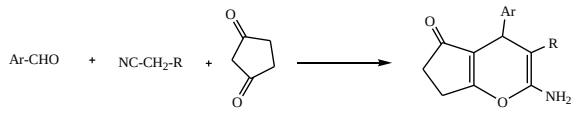


151 **152** **153**

X: (a) O, (**b**) NH

Yao and co-workers[80] reported a rapid and facile synthesis of cyclopenta [*b*] pyran derivatives namely, 2-amino-4-aryl-5-oxo-tetrahydrocyclopenta [*b*] pyran-3-carbonitriles (**156a**,**c**) and ethyl-2-amino-4-aryl-5-oxo-tetrahydrocyclo-penta[*b*]pyran-3-carboxylates (**156b**,**d**) under solvent free conditions by triturating a mixture of the three components;

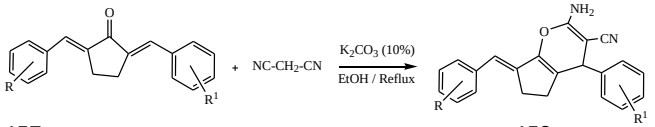
aromatic aldehydes (**154a**,**b**), malononitrile/ethyl cyanoacetate and cyclopentadione (**155**) at 80 °C.



154 **155** **156**

Ar: (**a**) C_6H_5, (**b**) C_6H_5, (**c**) ClC_6H_4, (**d**) ClC_6H_4, **R:** (**a**) CN, (**b**) COOEt, (**c**) CN, (**d**) COOEt

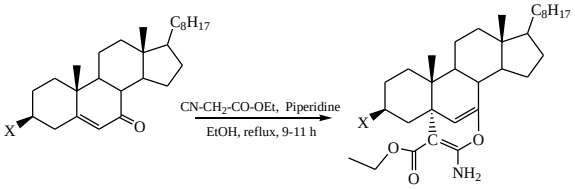
Karimi-Jaberi and Pooladian[81] synthesized a series of substituted 2-amino-4H-pyran-3-carbonitriles (**158a-s**) through a one-pot condensation of malononitrile and *α*,*α*'-*bis*(arylidene)cyclopentanones (**157a-s**) in ethanol by using K_2CO_3 as a catalyst. Short experimental reaction times, excellent yields, no need to use cumbersome apparatus for purification of the products, inexpensiveness and commercially availability of the catalyst were the advantages of this method.



157 **158**

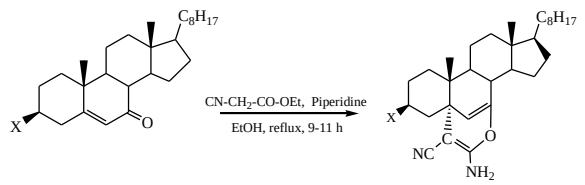
R: (**a**) CH_2, (**b**) CH_2, (**c**) CH_2, (**d**) C_2H_4, (**e**) C_2H_4, (**f**) C_2H_4 , (**g**) C_2H_4, (**h**) C_2H_4, (**i**) C_2H_4, (**j**) C_2H_4, (**k**) C_2H_4, (**l**) C_3H_6, (**m**) C_3H_6, (**n**) C_3H_6, (**o**) C_3H_6, (**p**) C_3H_6, (**q**) C_3H_6, (**r**) C_3H_6, (**s**) C_3H_6, **R^1:** (**a**) 2-Cl, (**b**) H, (**c**) 2-Cl,4-Cl, (**d**) 2-Cl, (**e**) H, (**f**) 2-Cl,4-Cl, (**g**) 4-F, (**h**) 4-Br, (**i**) 4-OMe, (**j**) 4-Me, (**k**) 2-Cl,6-F, (**l**) H, (**m**) 2-Cl, (**n**) 2-Cl,4-Cl, (**o**) 4-F, (**p**) 4-Br, (**q**) 4-OMe, (**r**) 4-OMe, (**s**) 2-Cl,6-F

Shamsuzzaman and co-workers[82] reported the reaction of steroidal ketones (**159-161**) with ethyl cyanoacetate that provided substituted steroidal 4H-pyrans (**162-164**) in better yields.



X: OAc(**159**), Cl(**160**), H(**161**) X: OAc(**162**), Cl(**163**), H(**164**)

Shamsuzzaman and co-workers[83] also reported the reaction of steroidal ketones (**159-161**) with malononitrile that gave cyano appended steroidal 4H-pyrans (**165-167**) in good yields.



X: OAc(**159**), Cl(**160**), H(**161**) X: OAc(**165**), Cl(**166**), H(**167**)

Conclusion

In this article we have mentioned the different routes for the synthesis of pyrimidine and pyran derivatives. The steps included condensation followed by cyclization or multi component reaction (MCR), either in a step-wise manner or in one pot has been achieved successfully to obtain the aforementioned two classes of heterocycles under different conditions. Most of the preparative methods included diethyl oxalate, diethyl malonate, malononitrile and ethyl cyanoacetate as the common reagents for the synthesis of pyrimidines and pyrans appended on different heterocyclic skeletons. Also many series of substituted pyrimidine and pyran-fused six membered heterocycles possessing *N*-, *S*- and *O*- have been constructed in potential yields and with conventional methods. Hence these protocols provide convenient strategies to annelate different heterocyclic nuclei with widespread bioactive pyrimidines and pyrans thereby extending the categories of heterocyclic systems. These strategies may also provide valuable information for the further design and development of more active biological agents through various modifications and derivatizations.

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